DIFFUSION TENSOR IMAGING OF TRAUMATIC BRAIN INJURY

Pratik Mukherjee

Departments of Radiology and Bioengineering,
University of California, San Francisco, CA

Corresponding Author:

*Pratik Mukherjee, M.D., Ph.D.

Department of Radiology, Neuroradiology Section

University of California, San Francisco

505 Parnassus Avenue, Box 0628

San Francisco, California 94143-0628

Phone: (415) 353-1537

Fax: (415) 353-8593

Email: pratik@radiology.ucsf.edu

Traumatic brain injury (TBI) is a leading cause of mortality and morbidity in Americans, especially those under age 45. TBI accounts for more than 500,000 emergency department visits annually (Nirula *et al.*, 2003). Closed head injury produces cerebral edema, hemorrhage, contusions, and ischemia. Diffuse axonal injury (DAI) is also a common consequence of head trauma, and results from rotational acceleration and deceleration forces that shear axons. DAI causes loss of consciousness at the moment of direct impact. More chronically, DAI can result in long-term cognitive and psychiatric problems.

Accurate evaluation of traumatic white matter injury is limited because conventional imaging techniques (a) tend to underestimate of the extent of injury; (b) often provide inadequate localization of axonal shearing within specific white matter tracts, for correlation with functional deficits; and (c) do not provide quantitative pathophysiological information that could be used to determine prognosis and to monitor the efficacy of therapeutic interventions. For the detection of DAI, CT is mostly limited to depicting the small focal hemorrhages associated with axonal shearing injury. Gradient echo T2*-weighted MR improves on CT through its better sensitivity to blood products, thereby demonstrating more lesions (Huisman *et al.*, 2003). However, pathologic studies demonstrate that only a minority of DAI lesions is associated with hemorrhage (Adams, 1984). Spin echo T2-weighted MR techniques, especially fluid-attenuated inversion recovery (FLAIR) imaging, can detect many non-hemorrhagic foci of DAI (Hesselink *et al.*, 1988; Mittl *et al.*, 1994; Ashikaga *et al.*, 1997) but still underestimate the true extent of traumatic white matter damage.

Diffusion-weighted imaging (DWI), which assesses the microscopic motion of water molecules in brain tissue, has improved the evaluation of TBI, especially for DAI, through its superior sensitivity to foci of acute shearing injury (Liu *et al.*, 1999; Huisman *et al.*, 2003). The mean diffusivity (D_{av}) can be calculated as the spatially-averaged magnitude of water diffusion at each voxel of the diffusion-weighted image. The D_{av} is most often decreased in acute axonal shearing injury, signifying reduced water diffusion, but can be increased or unchanged in a minority of lesions (Huisman *et al.*, 2003). Diffusion tensor imaging (DTI) offers additional advantages beyond older DWI techniques for the evaluation of traumatic axonal injury, through the sensitivity of quantitative measures such as fractional anisotropy (FA) to white matter integrity, as well as the ability of DTI to determine fiber orientations and delineate the 3-dimensional course of white matter pathways (Pierpaoli *et al.*, 1996; Conturo *et al.*, 1999; Mori *et al.*, 1999; Basser *et al.*, 2000).

These capabilities suggest that DTI may add value to conventional neuroimaging in patients with TBI. A pilot DTI study has shown that FA may be even more sensitive for detecting acute DAI than conventional MR imaging or DWI (Arfanakis *et al.*, 2002). Three-dimensional DTI fiber tractography has also been applied to delineate white matter pathways damaged by acute traumatic axonal shearing, with correlation to the resulting functional deficit (Le *et al.*, 2005a). Quantitative DTI parameters such as FA that reflect the microstructural characteristics of white matter may have prognostic value for patients with TBI. Indeed, in 20 acute TBI patients, FA showed better correlation with clinical outcome markers at hospital discharge than did D_{av} (Huisman *et al.*, 2004). Early changes in DTI parameters within a mean of 4 days after trauma was also found in another cohort of 20 patients, providing further support for the use of DTI as an early prognostic indicator of traumatic brain damage (Inglese *et al.*, 2005).

DTI has been improved by the convergence of many recent technical advances, including high-field at 3T, high angular resolution with dozens of diffusion-encoding directions, multi-channel phased-array head coils, and parallel imaging. The use of high angular resolution for DTI produces more accurate measurements of fractional anisotropy than does using the minimum of six diffusion-encoding directions necessary to solve for the diffusion tensor, even if those six directions are repeated many times and averaged for improved SNR (Jones, 2004). Both 3T and multi-channel head coils result in improved SNR over what can be achieved at 1.5T with a traditional quadrature birdcage head coil. Furthermore, the multi-channel head coils permits parallel imaging (Sodickson & Manning, 1997; Pruessmann *et al.*, 1997). Whereas parallel imaging degrades SNR for most pulse sequences, it can actually further boost SNR in single-shot EPI diffusion imaging with a judicious choice of acquisition parameters (Jaermann *et al.*, 2004). Parallel imaging performance also improves at high field, for a number of reasons that have been described in detail (Ohliger *et al.*, 2003; Pruessmann, 2004), but is beyond the scope of this brief review. Using high angular resolution 3T DTI with parallel imaging, whole-brain coverage at 1.8-mm isotropic spatial resolution has been achieved in a study of TBI (Le et al., 2005b). In this study, the greatest benefit of parallel imaging for 3T DTI was the striking reduction in susceptibility artifacts, which are particularly evident near tissue-air interfaces around the paranasal sinuses and mastoid sinuses. This enables imaging of the inferior frontal lobes, temporal lobes, brainstem, and cerebellum with high anatomic fidelity, which was previously not possible with high-field DTI using single-shot EPI. These regions near the skull base, especially the inferior frontal and temporal lobes, are the most common sites for contusions. Susceptibility artifacts due to hemorrhage or metallic surgical hardware are also

mitigated by parallel image acquisition. Thus, TBI represents an important clinical application for DTI using parallel imaging.

At the current time, however, there is no consensus on the optimal method for detecting and analyzing DTI abnormalities in the setting of TBI. Detecting abnormalities on FA maps of the brain can be more challenging than for conventional MR images. Arfanakis et al. (1999) have observed in 5 mild TBI patients that the reduced FA caused by traumatic damage can be difficult to perceive by visual inspection, especially when there is neighboring gray matter or CSF that also has low FA values. Evaluating white matter injury on conventional MR imaging involves qualitative assessment of signal intensity changes against a relatively uniform background within white matter. In contradistinction, optimal detection of white matter injury on FA maps requires quantitative measurements of a parameter that is strongly heterogeneous throughout the brain. Not only does FA vary between different white matter tracts in the normal human brain, but FA values also differ at various locations along a single white matter pathway. Whole-brain histograms of DTI parameters have been shown to be insensitive to TBI (Inglese *et al.*, 2005), and also discard the regionally specific information inherent to DTI. Prior quantitative DTI studies of TBI have used manually placed regions of interest (ROIs) to compare FA values between TBI patients and healthy volunteers (Arfanakis *et al.*, 2002; Huisman *et al.*, 2004; Le *et al.*, 2005a; Inglese *et al.*, 2005). This method of comparing DTI parameters in the same locations across subjects can be problematic, especially when applied to a patient population with marked heterogeneity in the location and extent of injury, such as in TBI. Other drawbacks of manual ROI-based analysis include problems with intra-rater and inter-rater reproducibility, as well as the fact that only a small minority of brain regions can be examined in a reasonable amount of time by a single operator.

Voxel-based analysis (VBA) represents an alternative approach and overcomes these last two limitations of manual ROI measurements, enabling automated reproducible statistical comparisons across subjects throughout the entire brain. VBA methods such as statistical parametric mapping (SPM) require sophisticated spatial registration and normalization of the images to remove anatomical confounds (Friston *et al.*, 1995; Ashburner & Friston, 2000). Traditionally, VBA has been utilized for group comparisons, in which a sample of experimental subjects is compared with a matched sample of healthy control subjects. This approach works best for diffuse disease processes that affect the entire brain or for focal disorders that affect similar anatomic regions across subjects. Application of VBA to the study of TBI is complicated by its spatial heterogeneity, which can impede or even preclude adequate co-registration and normalization of images from different patients. A related problem is the effect of diffuse volume loss or of mass effect from large lesions that distort the anatomy of the brain. Beyond a certain threshold, large anatomic deformations may prevent adequate spatial co-registration to the normative template for application of VBA. This failing of current VBA methods such as SPM may be addressed by more sophisticated techniques. For example, voxel-based normalization may be applied to the full diffusion tensor, rather than to parametric scalar maps calculated from the diffusion tensor, which may result in improved co-registration by incorporating additional information such as fiber orientation (Jones *et al.*, 2002; Park *et al.*, 2003; Xu *et al.*, 2003). Also, the newer deformation tensor-based morphometry may perform better than voxel-based methods in the presence of local or global anatomical distortions by "morphing" the patient's brain to the normative template (Studholme *et al.*, 2003, 2004).

A requirement for VBA is an appropriate template for the spatial registration and normalization process. Fractional anisotropy maps provide a good template because the excellent contrast between gray and white matter allows for reliable registration of images among subjects. Another important factor for VBA of DTI is the selection of an appropriate statistical threshold and cluster size for maintaining sensitivity to pathology while minimizing false positives. Since VBA involves comparisons among hundreds of thousands of voxels throughout the entire brain, steps must be taken to reduce the false discovery rate. One method is to select a high threshold for statistical significance. Another is to require that a minimum number of neighboring voxels, called a "cluster", exceed the threshold in order to attain statistical significance. Clustering is based on the rationale that pathology tends to be locally correlated rather than affecting isolated voxels widely separated in space. In general, optimum values of the threshold and cluster size will vary based on the SNR and spatial resolution of the DTI acquisition, the DTI parameter being analyzed, and the type of pathology under investigation. Smoothing of the images prior to normalization is often used in VBA to improve SNR, reduce inter-individual variability to facilitate image co-registration, and to help ensure a Gaussian distribution of intensities within a voxel to enable adequate statistical correction for false positive errors due to multiple comparisons (Ashburner & Friston, 2001). However, smoothing leads to a loss of spatial resolution which would limit detection of small lesions, and may actually lead to false positive results when applied to DTI (Jones *et al.*, 2005).

The primary benefits of voxel-based analysis of DTI over visual inspection or manual ROI analysis are its automated quantitative assessment of the entire brain and its operator independence. Unlike ROIs, in which certain regions have to be selected in advance for quantitation, VBA can detect pathology in previously unsuspected brain regions. With large numbers of subjects, VBA could be used to correlate quantitative DTI parameters with measures of functional outcome and neurocognitive performance. Since DTI can parcellate white matter tracts based on fiber orientation, it may be possible to determine which neural pathways co-vary with specific measures of functional ability. This approach may be especially powerful for longitudinal studies of therapeutic interventions, including rehabilitation. Hence, voxel-based methods may prove important for fully exploiting the potential of DTI for providing quantitative biomarkers of TBI.

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